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What's in a Guideline? Developing Collaborative and Sound Research Designs that Substantiate Best Practice Recommendations for Transgender Health Care

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Abstract
Transgender medicine presents a particular challenge for the development of evidence-based guidelines, due to limitations in the available body of evidence as well as the exclusion of gender identity data from most public health surveillance activities. The guidelines that have been published are often based on expert opinion, small studies, and data gathered outside the US. The existence of guidelines, however, helps legitimate the need for gender-affirming medical and surgical interventions. Research conducted on transgender populations should be grounded in gender-affirming methodologies and focus on key areas such as health outcomes after gender-affirming interventions.

Introduction

The past three decades have seen exponential growth in the range and depth of evidence-based guidelines in a broad range of medical disciplines [1]. The term "evidence-based medicine" first appeared in a brief article published in 1992 in the *Journal of the American Medical Association* (*JAMA*) by the Evidence-Based Medicine Working Group [2]. The article built on prior efforts to describe the development of guidelines that are accurate, accountable (to patients, science, and society), predictable (i.e., provide specific detail and figures), defensible (i.e., transparent about how they were developed and consensus was reached), and usable (in a range of real-world settings). These five key considerations in the development of evidence-based guidelines were summarized in an essay published in *JAMA* in 1990 [3].

Guidelines (also referred to as "best practices" or "standards of care") are generally developed through a consensus process involving a panel of experts (i.e., a multidisciplinary group of clinicians and methodological experts as well as representatives of populations likely to be affected) who evaluate available quantitative evidence gathered in a systematic manner, ideally filtered through a clinical lens, that is, with an eye to its applicability in clinical practice [4]. A number of approaches to achieving expert consensus have been described [5]. Numerous criteria also have been developed to assess the strength of individual recommendations based on the quality of underlying evidence and its applicability to the current question at hand [6]. Relatedly,

the question of "what is a guideline?" has been explored, with some suggesting that there exists a threshold of evidential quality and relevance below which only "good practice recommendations"—rather than guidelines—can be made [7]. The purpose of evidence-based guidelines is ultimately to improve health outcomes by both supporting clinical care of individual patients and informing the development of specific quality and outcome measures for patient care that permit meaningful surveillance of a particular practice, specialty, or health care delivery system.

The existence of guidelines in the field of transgender medicine both legitimizes the need for gender-affirming medical and surgical interventions and informs medical practitioners and policymakers on how to best meet these needs. Transgender medicine presents a particular challenge for the development of evidence-based guidelines. First and foremost, data on health outcomes in transgender medicine are currently limited to retrospective studies, case series, and individual case reports due to the lack of funding opportunities for research in this field as well as institutional stigmatization of the transgender community [8, 9]. In addition, the lack of uniform data collection by gender identity renders much of the population effectively invisible in health outcome surveillance efforts [10, 11]. Furthermore, academic transgender medicine programs are in their infancy [12], with the exception of several well-established centers in Europe and a few nascent programs in the United States, and there is a general lack of research and clinical fellowship training programs. This has resulted in little opportunity for the body of scientific evidence and academic infrastructure in the field to achieve the level needed to support the development of evidence-based guidelines.

Current Guidelines for Transgender Medicine

The primary set of reference guidelines in the field of transgender medicine has been the World Professional Association for Transgender Health (WPATH) *Standards of Care* (*SOC*) [13]. Currently in its seventh version (*SOC* v7), the *SOC* debuted in 1979 as a set of recommendations for the diagnosis of what the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) now refers to as gender dysphoria (distress experienced by transgender people when their gender identity has not been affirmed through social, medical, and/or surgical transition), previously referred to as "gender identity disorder" or "transsexualism" [14], and for the assessment of a person's readiness and eligibility to access a variety of medical and surgical interventions for gender affirmation, such as hormone therapy or genital surgery [15]. Over the years, this document has evolved substantially, yet it remains largely based on lower-quality evidence (i.e., observational studies) and expert opinion, and with a scope that remains limited primarily to describing best practices for the diagnosis of gender dysphoria and assessing readiness and appropriateness for interventions. *SOC* v7 lacks any rating of the quality of the available evidence or strength of the recommendations or description of how expert contributors are selected to participate in the process of developing the guidelines.

Despite their limitations, the *SOC* has played an essential role in advancing transgender health by legitimizing transgender identities and serving as a reference point for policymakers and health insurance payers seeking guidance on how to respond to transgender health needs. In the US, expanded access to gender-affirming medical and surgical interventions by patients using Medicare [16] and insurance plans covered by the Patient Protection and Affordable Care Act [17] has been driven by the very existence of the *SOC*. Recent changes to the *DSM-5* [18], the removal of gender dysphoria as a mental health condition in France [19], and the current consideration by the World Health Organization (WHO) to eliminate gender dysphoria from its list of mental health conditions, have all also been influenced by the *SOC* [20]. Taking a harm-reduction approach and in refutation of those who argue for a minimum threshold setting the boundary between a guideline (or standard of care) and a weaker good practice recommendation [6], the absence of high-quality evidence should not serve as an immutable barrier to developing meaningful consensus guidelines in a field where societal stigmas have served as the principal underlying reason for the lack of quality evidence.

In addition to the WPATH *SOC*, a number of other guidelines, protocols, and best practice recommendations have been published in the peer-reviewed literature as well as in the public domain; others are behind proprietary paywalls [21, 22]. These guidelines range from rudimentary online documents intended for internal use at a specific organization to a comprehensive set of recommendations with background information and citations. One particularly rigorous and complete set of guidelines are the recently revised University of California, San Francisco (UCSF) *Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People*, second edition [23]. These guidelines consist of nearly 200 pages of fully referenced expert consensus recommendations, developed using an intentional consensus building round-robin approach, peer reviewers for each topic, community input, and a grading scheme adapted from the GRADE system, a globally recognized approach to evaluating evidence based on the quality of available studies and providing a rating for the strength of recommendations [24]. Through this rigorous process, the UCSF guidelines meet the criterion of evidence-based.

In addition to following a process that insured that the UCSF guidelines would be evidence-based as well as accurate, accountable, predictable, and defensible, the authors of the UCSF guidelines also took steps to ensure that the guidelines would be usable in real-world clinical settings. The list of topics for inclusion and revision in the UCSF guidelines were developed in part based on several years of user feedback, which included specific questions for clarification or regarding omission of specific topics. The panel of individual contributors comprised experts from a broad range of disciplines, degrees, and practice settings, including academic medical centers, safety-net and

homeless clinics, and large managed care health systems. Input was also sought from community members and nonclinical academics for broader validity checking.

Creating Stronger Practice Guidelines for Transgender Health

Current limitations. There are several key areas where data needed to inform high-quality guidelines are lacking. Unanswered questions remain regarding the long-term outcomes of hormonal and surgical interventions as well as the comparative safety and efficacy of different approaches to hormone therapy [9]. Most research on the long-term effects of hormones has been conducted in Europe, where hormonal regimens differ from those in the US and other regions [22, 25]. Additionally, these studies were conducted among fairly homogenous populations that lack the racial, ethnic, and socioeconomic diversity found in the US. Thus these findings might not provide the best evidence on which to base guidelines for a demographically heterogeneous country like the US where different hormonal regimens are used.

There are also few studies investigating potential drug-drug interactions between the formulations of estrogens commonly used in some medically assisted gender transition and other drugs like those used for the treatment or pre-exposure prophylaxis of HIV infection or hepatitis C [26]. Although some studies, mostly small and cross-sectional in design, have suggested that mental health is improved by gender-affirming care [27, 28], larger longitudinal studies on mental health and quality-of-life outcomes are needed to inform policies that would support making gender-affirming care more available and accessible and to develop best practices for the delivery of such care [29].

Evaluating health outcomes for hormonal therapies is further complicated by methodological issues such as inconsistent (or lack of) comparison groups, uncontrolled confounding factors, small sample size, difficulty accessing the population [30] and high rates of loss to follow-up (more likely among those facing homelessness or housing instability), short follow-up period, and the need to evaluate a wider range of health outcomes (e.g., physical and mental health, social functioning, and quality of life). Randomized controlled trials (RCT), particularly if they are double-blinded and conducted at multiple centers to enroll large numbers of participants, are considered the strongest study design (i.e., the highest level of scientific evidence) to evaluate the causal effects of interventions on health outcomes. However, individual RCTs might not always be feasible or ethically acceptable [31], including in transgender medicine and clinical research. For example, randomizing transgender people to receive or not receive hormone therapy would violate the principle of equipoise, the idea that there is true scientific uncertainty about whether an intervention will benefit a patient-participant, since evidence suggests that hormone therapy is helpful at alleviating gender dysphoria [27, 28]. Nevertheless, there are additional research questions that can be investigated using RCTs. In particular, research can be designed and clinical trials implemented to compare different delivery modes and schedules for hormone treatment.

Improving research on transgender health. Transgender medicine would benefit from well-designed and rigorous observational comparative studies, which use more patients' data and longer follow-up periods than RCTs in addition to being less costly to conduct [32]. To conduct this research—and to guide provision of competent transgender clinical care—will require validated, standardized, gender-affirming clinical tools for a range of measures, including a history of hormonal or surgical care or accessing gender-affirming care outside of professional settings, which will simultaneously guide provision of trans-competent clinical care [12]. As these research recommendations suggest, patient-centeredness is a critical component of transgender health research. This means working "with," not "on," transgender communities in the design, methods, conduct, and dissemination of studies to inform evidence-based clinical care [33]. Meaningful transgender community engagement will ensure that the research is ethical and acceptable to transgender people and will also ensure study feasibility by fostering trust and synergy between researchers and local communities. Another concern is that individual-level randomization of transgender women in HIV prevention studies to either intervention groups or control groups could likely separate women who are socially connected and mutually supporting, with the result that the study would fail to harness existing community networks and structures that could facilitate intervention uptake (should the intervention prove to be beneficial) or bolster intervention effects.

Routine collection of gender identity data for research purposes will facilitate the conduct of high-quality observational research [33] as well as inform policymakers on the true size and nature of the transgender population, facilitating appropriate research funding allocation. More specifically, it would enable the pooling of transgender patient data from across clinics, community health centers, hospitals, and practices to create large multisite longitudinal cohorts. The use of such cohorts in transgender research would support the development of specific quality and outcome measures for transgender patient care, which in turn could support the development of evidence-based guidelines to improve the quality of clinical practice and training in transgender medicine.

Lastly, the National Institutes of Health and other research funding agencies should begin to recognize transgender status as an independent predictor of health disparities, permitting access to funding streams specifically focused on disadvantaged or minority groups and their specific vulnerabilities.

Conclusion

The expanded visibility of and the medical community's awareness of the health care needs of transgender people has developed more quickly than has the development of evidence-based guidelines and standards for treatment of this population. A pipeline of new research, driven by a workforce of investigators with specific training in transgender

health, is needed to support the health care of this increasingly visible community. Any guidelines that are produced should be grounded in the same high-quality standards that are expected in other fields of health sciences, using available data and extrapolation of data from other fields. Specific research on outcomes related to gender-affirming care and the impact of such care on the natural history and management of HIV or hepatitis is of the utmost importance. Clinical tools and research methods should be transgender-affirming, patient-centered, and engage community participation. Above all, gender identity data must be collected uniformly and consistently in order to inform funding mechanisms and increase the availability of resources and support for research and other scholarly activity aimed at improving the health of transgender people.

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